Please add the following claims.

--10. A method to treat hyperphosphataemia in a subject which method comprises administering to said subject an amount of lanthanum carbonate of the formula

$$La_2(CO_3)_3 \cdot xH_2O$$

wherein x has a value from 3 to 6

effective to treat said hyperphosphataemia.

11. The method of claim 10 wherein x has a value from 3.5 to 5.

12. The method of claim 11 wherein x has a value from 3.8 to 4.5.

13. The method of any of claims 10-12 wherein said administering is by an oral route.--

REMARKS

The claims have been amended to conform to U.S. practice, obviate the rejection under 35 USC 101, and more particularly point out the invention. New claims 10-13 are supported on page 3, beginning at line 20 and throughout the specification. No new matter has been added and entry of the amendment is respectfully requested.

The Invention

The invention resides in the unexpected discovery that lanthanum carbonates with waters of crystallization or hydration between 3 and 6 moles of water per mole of lanthanum carbonate are particularly effective in absorbing phosphate both *in vivo* and *in vitro*. This ability finds practical use in treating patients whose phosphate levels in the blood are too high. Rapid binding is extremely important because the drug is generally administered with food and must bind phosphate in the food before the phosphate is absorbed into the bloodstream. Further, the binding must take place at acidic conditions associated with the stomach. The rapid binding at very low levels of the lanthanum carbonate hydrates of the invention permit acccptable dosage

levels and patient acceptance. Accordingly, the claims are directed to methods of treating hyperphosphataemia using the phosphate hydrates of the invention and pharmaceutical compositions for administering these hydrates. Nothing in the cited art suggests the use of lanthanum carbonate with waters of hydration in the range of 3-6 in this manner.

The Rejections

The rejections of claims 5, 6 and 9 on formal grounds are believed obviated. Due to the cancellation of claim 4, claim 5 no longer depends on a multiply dependent claim. Claims 6 and 9 have been canceled. Claim 6 has been replaced by new claim 10 which is in U.S. format and recites a positive step. Accordingly, these bases for rejection can be withdrawn.

Further, claim 9 was rejected as assertedly anticipated by several documents. Claim 9 has been canceled.

The remaining rejections are under 35 USC 103.

All claims, claims 1-9, were rejected as obvious over Junji (JP 62/145024).

Applicants assume that the evaluation by the Office of Junji is based on the abstract which indicates that carbonates or inorganic acid compounds of rare earth elements such as Y, La, Ce, Pr, etc. are used as immobilizing agents for phosphate ions. The abstract suggests that such compounds would be useful in treating hyperphosphataemia. However, the abstract also indicates that the immobilizing agents immobilize and remove phosphate well only at pH levels above 6. Clearly, this is disadvantageous as the pH conditions in the stomach are much lower.

Further, as the Office points out, Junji merely discloses a large genus of salts, of which the claimed hydrates are only a single subspecies. It has been held at least twice by the Federal Circuit that disclosure of a genus of this type does not render unpatentable an undisclosed species. For example, in *In re Baird*, 16 F.3d 380, 29 USPQ2d 1550 (Fed. Cir. 1994), claims to copolymers formed from a specific diol and diacid chosen from a list of three specific dicarboxylic acids were held patentable over a genus which included these species. In *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941, 1944 (Fed. Cir. 1992), a particular ammonium salt of the herbicide dicamba was held patentable over the disclosure of a genus which included this salt. Copies of these decisions are attached for the convenience of the Office.

While there may be a certain logic to the Examiner's reasoning that it would have been obvious to pick any arbitrary species of the genus taught by Junji and have expected it to work,

this is not the position taken by the Federal Circuit. And clearly, there is no expectation that the members of this species would work dramatically better than the remaining members of the genus.

Here, there is no specific disclosure of $La_2(CO_3)_3 \cdot xH_2O$ where x has a value from 3-6 in the Junji document. While generically included in the abstract, this specific species is clearly not suggested. Thus, there is not even a *prima facie* case that these specific hydrates are obvious for use as pharmaceuticals.

Further, the specification supporting these claims demonstrates that these species show unexpected results. For example, Figure 1 shows the percent phosphate removal at 5 minutes obtained when lanthanum carbonate at various levels of hydration is used in the experiment set forth on page 6 of the specification. In this *in vitro* experiment, a solution at pH 3, close to the pH level found in the digestive tract was used. Sample 1 has water of hydration such that x=8.8. In Sample 2, x is 1.3. Sample 3 contains 4.4 waters of hydration. Clearly sample 3 is far superior. More detailed data are seen in Table 1 on page 7 which show that after only two minutes sample 6, which has 3.8 waters of hydration, has already removed 88.1% of the phosphate from solution whereas sample 2 has removed only 28.1%. In Table 1, Sample 1 has 8.8 waters of hydration, Sample 2 has 1.3, Sample 3 has 4.4, Sample 4 has 2.2, Sample 5 has 4, and Sample 6 has 3.8.

These unexpectedly excellent results for lanthanum carbonate in the claimed range of hydration clearly support patentability of methods to treat hyperphosphataemia with these compounds. And the specification at page 12 demonstrates that *in vivo*, the hydrated form is successfully excreted and does not pass into the circulation system.

Applicants appreciate the indication at the interview that claims directed to a method to treat hyperphosphataemia, claims 10-13 appear allowable.

The Office has pointed to no description in Junji or elsewhere of the method of preparation of the desired hydrates set forth in claims 7 and 8. There appears to be no cited document which describes this method of preparation. Applicants appreciate the indication at the interview that claims 7 and 8 are allowable as well.

Applicants understand from the discussion at the interview that the rejection of claims 1-3 and 5 are based primarily on the assumption that the individual documents Yanagihara, Mineely and Mzareulishvili inherently imply compositions that could be used as pharmaceutical

compositions and that the intended purpose for the pharmaceutical compositions does not confer patentability. But applicants do not rely on any specific intended purpose to distinguish these documents. *This is not an instance where the prior art has disclosed pharmaceutical compositions of a compound for a different indication and the new indication is relied upon for patentability. This is a situation where the cited documents do not suggest pharmaceutical compositions of any kind.* These documents teach individually the lanthanum carbonate hydrates wherein x is 5, 3 and 6 respectively. The Office takes the view that because these specific compounds may be diluted in water, water represents a pharmaceutical excipient and places these within the scope of the claims. It is respectfully submitted that this is an error. These documents are strictly directed to the chemistry of the hydrates *per se* and make no suggestion that the hydrates be formulated for administration to individuals, or even that they be added to water.

Respectfully, it should be noted that there is a good deal more to preparing a pharmaceutical composition than simply dissolving an active ingredient in water. Special precautions must be taken to maintain sterility; only certain pharmaceutically acceptable excipients can be used; the amounts of the materials must be adjusted to obtain reasonable dosages, and the preparation must be free of any materials that might be deleterious to the patient. None of the documents cited implies that any such precautions should be taken or that formulations of the specified hydrates be prepared in accordance with good manufacturing practices or with any other suitable precautions that would be required for pharmaceutical compositions.

None of the cited documents even suggests combining lanthanum carbonate hydrate with water. In Yanagihara the pentahydrate is prepared by autoclaving the oxide with CO_2 in aqueous solution. The resulting lanthanum carbonate (one of many compounds prepared among other lanthanides) is precipitated from solution. The resulting precipitate is simply analyzed. There is no suggestion of formulating this precipitated material in any way that would be suitable for administration to a patient. In Mineely the reaction of the trihydrate with molten $K_2S_2O_7$ was studied. Water is not mentioned. The resultant is that the correspondent sulfate is formed. There is nothing in Mineely that suggests formulating any lanthanum carbonate or any other of the lanthanides studied to obtain a composition which could safely be administered to subjects. In Mzareulishvili the reaction of lanthanum nitrate with various carbonates was studied and

found to yield the hexahydrate in a complex mixture with other salts. There is no suggestion that any of the products be combined with water. It is highly unlikely that such a complex mixture would be considered useful even as a starting point for formulation of the hexahydrate to be administered to subjects.

Thus, it cannot fairly be said that the Yanagihara, Mineely, or Mzareulishvili documents suggest pharmaceutical compositions of these species. None of the documents suggests any composition that could remotely be considered suitable for administration to a patient.

Applicants call the attention of the Office to the attached decision in *In re Wiggins*, 158 USPQ 199 (CCPA 1968) which addresses a similar issue. In that case, the claimed compositions were held patentable over a document which actually disclosed compositions that were useful for administration to subjects. The cited document taught away from the claimed method of use, but the Board of Appeals has held that the pharmaceutical compositions themselves were suggested by this earlier document. Wiggins overcame this rejection at the CCPA with the argument that the document did not suggest the dosage levels required in the claims. Thus, as the Court put it,

> We find nothing in Wolf which suggests that he or any other person of ordinary skill in the art would regard the preparation or administration to mice or humans of compositions containing sufficiently greater amounts of "O_2" as to fall within the scope of the appealed claims to be obvious.

Thus, if the *nature* of the composition is sufficiently well defined that it is not suggested by the art disclosing the compound which is the active ingredient, the composition is patentable. In *Wiggins*, the cited documents failed to suggest the appropriate, claimed amounts of active ingredient. Here, the cited documents suggest none of the limitations that would be characteristic of the term "pharmaceutical" compositions, which limitations are thus required by claims 1 - 3 and 5.

The Examiner also states that the determination of dosage having the optimum therapeutic index is within ordinary skill. It is assumed that this is intended to address the further limitations of claim 5. Claim 5 is patentable for the same reasons set forth above; however, the enhanced efficiency of the claimed lanthanum carbonate hydrates permits these lower dosages.

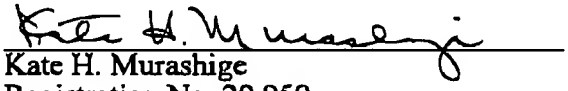
Thus, it is believed that claims 1-3 and 5 are not suggested by the art and are allowable.

Conclusion

The cited art fails to suggest the claimed methods of the invention (claims 10-13) which utilize lanthanum carbonate hydrates having waters of hydration in the particular range 3-6 which are particularly effective at absorbing phosphate at low pH. Nothing in the cited art points to these specific species for this use. Further, the claimed species are unexpectedly superior to other lanthanum carbonate hydrates. There is no cited document which purports to disclose the process claimed in claims 7 and 8. Further, since there is *nothing in the art which suggests the use of hydrates with this specific range for any pharmaceutical use whatsoever*, there is no suggestion in the art to prepare compositions which contain all the limitations inherent in pharmaceutical formulations -- including sterility, appropriate dose level, suitable excipients, and freedom from toxic ingredients. Accordingly, it is believed that claims 1-3, 5, 7, 8 and 10-13 are in a position for allowance and passage of these claims to issue is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 391442000200. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: November 19, 1998 By: 

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